PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No: 27129/33638A

CONTINUING APPLICATION TRANSMITTAL UNDER 37 CFR 1.53(b)

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a request under 37 CFR 1.53 for filing a

☒ continuation application.

☐ divisional application.

1. Particulars of Prior Application

Application Serial No:	08/756,164
Filed on:	November 25, 1996
Title:	METHOD OF TREATING CONDITIONS ASSOCIATED WITH INTESTINAL ISCHEMIA/REPERFUSION
Art Unit:	1646
Examiner:	D. Romeo
Prior Docket No.:	27129/33638

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this Continuing Application Transmittal Under 37 CFR 1.53(b) and the documents referred to as enclosed therewith are being deposited with the United States Postal Service on **October 12, 1999**, in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 utilizing the "Express Mail Post Office to Addressee" service of the United States Postal Service under Mailing Label No. EM 099 778 751 US.

Richard Zimmermann

2. This request is filed by:

1. Full Name of Inventor	Family Name Ammons	First Given Name William	Second Given Name Steve
Residence & Citizenship	City Pinole	State or Foreign Country California	Country of Citizenship United States of America
Post Office Address	Post Office Address 490 Dohrmann Lane	City Pinole	State & Zip Code/Country California 94564
2. Full Name of Inventor	Family Name Meszaros	First Given Name Karoly	Second Given Name M.
Residence & Citizenship	City San Ramon	State or Foreign Country California	Country of Citizenship Hungary
Post Office Address	Post Office Address 2938 Morgan Drive	City San Ramon	State & Zip Code/Country California 94583
3. Full Name of Inventor	Family Name	First Given Name	Second Given Name
Residence & Citizenship	City	State or Foreign Country	Country of Citizenship
Post Office Address	Post Office Address	City	State & Zip Code/Country

☐ This application is being filed by less than all the inventors named in the prior application. An accompanying statement requests deletion of the name(s) of the person(s) who are not inventors of the invention being claimed in this application.

3. **Amendments**

☒ Amend the specification by inserting before the first line the sentence:

--This is a **Continuation** of U.S. application Serial No. 08/756,164, filed November 25, 1996 which is a Continuation of 08/232,527, filed April 22, 1994.--

☐ Cancel claims in the prior application before calculating the filing fee.

☐ A Preliminary Amendment is enclosed.

☒ The filing fee is based upon entry of the foregoing amendment(s) (if any).

4. **Copy of Prior Application**

The enclosed is a copy of the prior complete application, including the specification (with claims), drawings, the oath or declaration, and any amendments referred to in the oath or declaration filed to complete the prior application.

5. **Incorporation By Reference**

The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under paragraph 4, above, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. **Priority**

☐ Priority of application No. _____, filed on _____ in _____ is claimed under 35 USC 119.

☐ The certified copy(ies) was(were) filed in prior U.S. application Serial No. _____.

☐ The certified copy(ies) has(have) not been filed.

7. **Assignment**

☒ The prior application is assigned of record to Xoma Corporation, and has been recorded at Reel No. 7626, Frame No. 99.

8. **Small Entity Status**

☐ Verified statement(s) claiming small entity status is(are) attached.

☒ Small entity status has been established in the prior application and is still proper and desired.

9. **Fee Calculation**

CLAIMS AS FILED - INCLUDING PRELIMINARY AMENDMENT (IF ANY)						
			SMALL ENTITY		OTHER THAN A SMALL ENTITY	
	NO. FILED	NO. EXTRA	RATE	FEE	RATE	FEE
BASIC FEE				$380.00		$760.00
TOTAL	10 -20	= 0	X 9 =		X 18 =	$
INDEP.	1 - 3	= 0	X 39 =		X 78 =	$
☐ First Presentation of Multiple Dependent Claim			+ 130 =		+ 260 =	$
			Filing Fee:	$380.00	**OR**	$

10. **Method of Payment of Fees**

☒ Attached is a check in the amount of: $380.00

☐ Charge Deposit Account No. 13-2855 in the amount of: $_____
A copy of this Transmittal is enclosed.

11. **Deposit Account and Refund Authorization**

The Commissioner is hereby authorized to charge any deficiency in the amount enclosed or any additional fees which may be required during the pendency of this application under 37 CFR 1.16 or 37 CFR 1.17 to Deposit Account No. 13-2855. A copy of this Transmittal is enclosed.

Please refund any overpayment to Marshall, O'Toole, Gerstein, Murray & Borun at the address below.

Please direct all future communications to Li-Hsien Rin-Laures,M.D., at the address below.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BORUN
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312) 474-6300
(312) 474-0448 (Telefacsimile)

By: _____
Michael F. Borun
Reg. No: 25,447

October 12, 1999

JOINT INVENTORS

APPLICATION FOR UNITED STATES LETTERS PATENT

SPECIFICATION

TO ALL WHOM IT MAY CONCERN:

Be it known that we, William Steve Ammons, a citizen of the United States of America, residing at 490 Dohrmann Lane, Pinole, in the County of Contra Costa and State of California, and Károly M. Mészáros, a citizen of Hungary, residing at 2938 Morgan Drive, San Ramon, in the County of Contra Costa and State of California, have invented a new and useful METHOD OF TREATING CONDITIONS ASSOCIATED WITH INTESTINAL ISCHEMIA/REPERFUSION, of which the following is a specification.

METHOD OF TREATING CONDITIONS ASSOCIATED WITH INTESTINAL ISCHEMIA/REPERFUSION

BACKGROUND OF THE INVENTION

The present invention relates to therapeutic uses of bactericidal/permeability-increasing (BPI) protein products for the treatment of adverse physiological effects associated with intestinal ischemia/reperfusion.

Reperfusion of ischemic intestines is associated with profound cardiovascular and respiratory dysfunction that may lead to shock and death. A variety of mediators are believed to be released from the ischemic tissue that could lead to cardiorespiratory collapse, including oxygen free radicals, protanoids, and platelet activating factor.

During ischemia, breakdown of the intestinal mucosal permeability barrier may result in translocation of endotoxin and/or bacteria from the intestinal lumen. Endotoxin has been detected in the portal vein after intestinal ischemia/reperfusion. However, a role for translocated bacteria or endotoxin in intestinal ischemia/reperfusion injury has not been clearly defined.

Bactericidal/permeability-increasing protein (BPI) is a protein isolated from the granules of mammalian PMNs, which are blood cells essential in the defense against invading microorganisms. Human BPI protein has been isolated from polymorphonuclear neutrophils by acid extraction combined with either ion exchange chromatography [Elsbach, *J. Biol. Chem.*, *254*:11000 (1979)] or *E. coli* affinity chromatography [Weiss, et al., *Blood, 69*:652 (1987)] referred to herein as natural BPI and has potent bactericidal activity against a broad spectrum of gram-negative bacteria. The molecular weight of human BPI is approximately 55,000 daltons (55 kD). The amino acid sequence of the entire human BPI protein, as well as the DNA encoding the protein, have been elucidated in Figure 1 of Gray et al., *J. Biol. Chem.*, *264*:9505 (1989), incorporated herein by reference.

The bactericidal effect of BPI has been shown to be highly specific to sensitive gram-negative species, while non-toxic for other

microorganisms and for eukaryotic cells. The precise mechanism by which BPI kills bacteria is as yet unknown, but it is known that BPI must first attach to the surface of susceptible gram-negative bacteria. This initial binding of BPI to the bacteria involves electrostatic interactions between the basic BPI protein and the negatively charged sites on lipopolysaccharides (LPS). LPS has been referred to as "endotoxin" because of the potent inflammatory response that it stimulates. LPS induces the release of mediators by host inflammatory cells which may ultimately result in irreversible endotoxic shock. BPI binds to Lipid A, the most toxic and most biologically active component of LPS.

In susceptible bacteria, BPI binding is thought to disrupt LPS structure, leading to activation of bacterial enzymes that degrade phospholipids and peptidoglycans, altering the permeability of the cell's outer membrane, and ultimately causing cell death by an as yet unknown mechanism. BPI is also capable of neutralizing the endotoxic properties of LPS to which it binds. Because of its gram-negative bactericidal properties and its ability to neutralize LPS, BPI can be utilized for the treatment of mammals suffering from diseases caused by gram-negative bacteria, such as bacteremia or sepsis. Bahrami et al., *Int'l Endotoxin Soc. Meeting*, Vienna, Austria (August 1992), disclose the use of a BPI protein for the treatment of hemorrhagic shock.

A proteolytic fragment corresponding to the N-terminal portion of human BPI holoprotein possesses the antibacterial efficacy of the naturally-derived 55 kD human holoprotein. In contrast to the N-terminal portion, the C-terminal region of the isolated human BPI protein displays only slightly detectable anti-bacterial activity. Ooi, et al., *J. Exp. Med., 174*:649 (1991). A BPI N-terminal fragment, comprising approximately the first 199 amino acid residues of the human BPI holoprotein and referred to as "$rBPI_{23}$", has been produced by recombinant means as a 23 kD protein. Gazzano-Santoro et al., *Infect. Immun. 60*:4754-4761 (1992).

SUMMARY OF THE INVENTION

The present invention provides novel methods for the treatment of adverse physiological effects associated with intestinal ischemia/reperfusion comprising administering BPI protein products to a subject suffering from the effects of intestinal ischemia/reperfusion. Specifically, the invention provides methods of treating the adverse physiological effects, including cardiac and hemodynamic effects, of intestinal ischemia/reperfusion resulting from a variety of causes. Such causes include mesenteric artery ischemia which is secondary to occlusions resulting from atherosclerosis, embolisms or arterial spasms; ischemia resulting from vessel occlusions in other segments of the bowel; ischemic colitis and intestinal torsion such as occurs in infants and particularly in animals. In particular, the invention provides methods for treating the adverse cardiac and other effects of intestinal ischemia and reperfusion associated with myocardial infarction.

The invention thus provides methods for treatment of sepsis-like conditions associated with intestinal ischemia/reperfusion comprising administering to a subject an amount of a BPI protein product effective to alleviate adverse physiological effects resulting from the presence of bacteria, bacterial particulates and endotoxin present in the body and in circulation in the blood.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts the hemodynamic effects of intestinal reperfusion;

Fig. 2 depicts the effects of a BPI protein product on reperfusion-induced hemodynamic dysfunction;

Figs. 3a and 3b depict the effects of a BPI protein product on hypotension resulting from intestinal ischemia/reperfusion;

Figs. 4a and 4b depict the effects of a BPI protein product on bradycardia resulting from intestinal ischemia/reperfusion;

Fig. 5 depicts the effects of a BPI protein product on respiratory depression resulting from intestinal ischemia/reperfusion;

Fig. 6 depicts the effects of a BPI protein product on arrythmias resulting from intestinal ischemia/reperfusion;

Fig. 7 depicts the effects of a BPI protein product on the survival time for rats subjected to intestinal ischemia/reperfusion; and

Figs. 8a and 8b depict the quantity of bacteria isolated from tissues of rats subjected to intestinal ischemia/reperfusion and the number of rats in which the bacteria were detected.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides methods of treatment of the adverse effects of intestinal ischemia/reperfusion by administering BPI protein products to subjects suffering from the effects of intestinal ischemia and reperfusion. According to one aspect of the invention, the adverse cardiac and hemodynamic effects including cardiac depression, arrthymia and hypotension associated with intestinal ischemia/reperfusion are alleviated by administration of effective amounts of BPI protein products. In particular, because these studies demonstrate the adverse cardiac and hemodynamic effects of intestinal ischemia/reperfusion, the administration of BPI protein products as an adjunctive therapy for the treatment of myocardial infarction would be particularly useful. The BPI protein products are preferably administered systemically such as intravenously, or by intramuscular or subcutaneous injection.

As used herein, "BPI protein product" includes naturally and recombinantly produced bactericidal/permeability-increasing protein; natural, synthetic, and recombinant biologically active polypeptide fragments of bactericidal/permeability-increasing protein; and biologically active polypeptide analogs or variants including hybrid fusion proteins, of either bactericidal/permeability- increasing protein or biologically active fragments thereof. The BPI protein products including biologically active fragments of BPI holoprotein which are to be administered according to the methods of this invention may be generated and/or isolated by any means known in the art.

U.S. Patent No. 5,198,541, the disclosure of which is hereby incorporated by reference, discloses recombinant genes encoding and methods for expression of BPI proteins. Co-owned, copending U.S. Patent Application Ser. No. 07/885,501 and a continuation-in-part thereof, U.S. Patent Application Ser. No. 08/072,063 filed May 19, 1993, which are hereby incorporated by reference, disclose novel methods for the purification of recombinant BPI protein products expressed in and secreted from genetically transformed mammalian host cells in culture, and discloses how one may produce large quantities of recombinant BPI products suitable for incorporation into stable, homogeneous pharmaceutical preparations.

Biologically active fragments of BPI include biologically active molecules that contain the same amino acid sequence as a BPI holoprotein, except that the molecule lacks amino-terminal amino acids, internal amino acids, and/or carboxy-terminal amino acids of the holoprotein. Amino-terminal fragments of BPI comprising up to about the first 200 amino acid residues of BPI are contemplated as being particularly useful according to the invention. By way of nonlimiting examples, such fragments include those described herein and a natural 25 Kd fragment and a recombinant 23 Kd, 199 amino acid residue amino-terminal fragment of the human BPI holoprotein referred to as $rBPI_{23}$. See, Gazzano-Santoro et al., *Infect. Immun. 60*:4754-4761 (1992). In that publication, an expression vector was used as a source of DNA encoding a recombinant expression product ($rBPI_{23}$) having the 31-residue signal sequence and the first 199 amino acids of the N-terminus of the mature human BPI, as set out in SEQ ID NOS: 1 and 2 taken from Gray et al., *supra*, except that valine at position 151 is specified by GTG rather than GTC and residue 185 is glutamic acid (specified by GAG) rather than lysine (specified by AAG). Recombinant holoprotein referred to herein as rBPI has also been produced having the sequence set out in SEQ ID NOS: 1 and 2 taken from Gray et al., *supra*, with the exceptions noted for $rBPI_{23}$.

Biologically active analogs and variants of BPI include, but are not limited to, recombinant hybrid fusion proteins comprising BPI holoprotein

or biologically active fragment thereof, and at least a portion of at least one other polypeptide. Such proteins are described by Theofan et al. in co-owned, copending U.S. Patent Application Serial No. 07/885,911, and a continuation-in-part application thereof U.S. Patent Application Serial No. 08/064693 filed May 19, 1993, which are incorporated herein by reference in their entirety and include hybrid fusion proteins comprising, at the amino terminal end, a BPI protein or a biologically active fragment thereof and, at the carboxy terminal end, at least one constant domain of an immunoglobulin heavy chain or allelic variant thereof.

Biologically active analogs and variants of BPI also include, but are not limited to, BPI protein products wherein one or more amino acid residues have been replaced by a different amino acid. For example, co-owned, copending U.S. Patent Application Ser. No. 08/013,801 (Theofan et al., "Stable Bactericidal/Permeability-Increasing Protein Products and Pharmaceutical Compositions Containing the Same," filed February 2, 1993) which is incorporated herein by reference, discloses polypeptide analogs of BPI and BPI fragments wherein a cysteine residue at position 132 or at position 135 is replaced by a different amino acid. A preferred BPI protein product described by this application comprises the first 199 amino acids of BPI holoprotein but wherein the cysteine at residue number 132 is substituted with alanine and is designated $rBPI_{21}\Delta cys$.

The administration of BPI protein products is preferably accomplished with a pharmaceutical composition comprising a BPI protein product and a pharmaceutically acceptable diluent, adjuvant, or carrier. The BPI protein product composition may be administered without or in conjunction with known surfactants, other chemotherapeutic agents or additional known antibiotics. A preferred pharmaceutical composition containing BPI protein products comprises BPI at a concentration of about 1 to 2 mg/ml in citrate buffered saline (0.02 M citrate, 0.15 M NaCl, pH 5.0) comprising 0.1% by weight of poloxamer 188 (Pluronic F-68, BASF Wyandotte, Parsippany, NJ) and 0.002% by weight of polysorbate 80 (Tween

80, ICI Americas Inc., Wilmington, DE). Such preferred combinations are described in co-owned, copending, U.S. Patent Application Ser. No. 08/190,869 filed February 2, 1994 which is a continuation in part of U.S Patent Application Ser. No. 08/012,360 (McGregor et al., "Improved Pharmaceutical Composition" filed February 2, 1993), the disclosures of which are incorporated herein by reference.

Other BPI protein products useful according to the methods of the invention are BPI peptides such as those described in co-owned and copending U.S. Patent Application Ser. No. 08/209,762 filed March 11, 1994 which is a continuation-in-part of U.S. Patent Application Ser. No. 08/183,222 filed January 14, 1994 which is a continuation-in-part of U.S. Patent Application Ser. No. 08/093,202 filed July 15, 1993 which is a continuation in part of U.S. Patent Application Ser. No. 08/030,644 filed March 12, 1993 the disclosures of which are hereby incorporated by reference.

Practice of the methods of the present invention is illustrated in the following examples wherein: Example 1 discloses the effect of administration of a BPI protein product on blood pressure, heart rate and respiratory rate of rats subjected to intestinal ischemia/reperfusion. Example 2 discloses the effect of administration of a BPI protein product on the translocation of bacteria in rats subjected to intestinal ischemia/reperfusion.

EXAMPLE 1

A rat surgical model was used to evaluate the effects of BPI protein products on the physiological effects associated with intestinal ischemia/reperfusion. Specifically Sprague Dawley rats were anesthetized with a mixture of 80 mg/kg of ketamine and 4 mg/kg of xylazine administered by intraperitoneal injection. After a surgical plane of anesthesia was obtained, a tracheotomy was performed and a tracheal cannula was inserted. The animals breathed on their own. A catheter, made of polyethylene tubing, was placed in a femoral artery. The catheter was connected to a pressure transducer in

order to measure blood pressure. Another catheter was placed in a femoral vein and connected to an infusion pump.

The abdominal contents were then exposed via a midline abdominal incision. The superior mesenteric artery (SMA) was visualized at its junction with the abdominal aorta and a silk ligature was threaded around the SMA after it had been gently loosened from the surrounding connective tissue. The loose ends of the ligature were placed outside the animal and the abdominal incision was then closed with surgical staples.

After surgery, the cardiac indices of blood pressure and heart rate were electronically recorded by measurement at the femoral artery and respiration rate was determined by visual observation for a period of about 30 to 45 minutes so that all recorded variables were stable. The ligature around the SMA was then tightened by until the SMA was occluded. The SMA remained occluded for 90 minutes at which time the ligature was loosened to allow reperfusion. Sixty minutes after the SMA was occluded 7 rats received an intravenous bolus injection of $rBPI_{21}\Delta cys$ in a vehicle comprising citrate buffered saline (0.02 M citrate, 0.15 M NaCl, pH 5.0) comprising 0.1% by weight of poloxamer 188 and 0.002% by weight of polysorbate 80 followed by a constant infusion of 2 mg/kg/hr. Seven other control rats received equal volumes of vehicle. The infusions continued until death.

Typical blood pressure and heart rate records for individual untreated and BPI treated rats are presented in Figs. 1 and 2 respectively. Opening the SMA occlusion after 90 minutes resulted in rapid declines in blood pressure and heart rate of all rats treated with vehicle. Within a few minutes, the heart rate of all but one control rat began to oscillate, partially in phase with respiration, but also in a slower, more irregular pattern. In 5 of the 7 control rats there appeared to be missed beats which are presumably the result of arrhythmias. In contrast, irregularities of heart rate and arrhythmias were seldom observed in $rBPI_{21}\Delta cys$ treated rats. Administration of $rBPI_{21}\Delta cys$ did have an effect in reducing the hypotension resulting from intestinal ischemia/reperfusion as shown by the results in Figs. 3a and 3b

where Fig 3a shows the results for both the ischemic and reperfusion phases of the experiment and Fig. 3b shows only the period of reperfusion. Data are shown for the first 30 minutes after opening the occlusion because all vehicle-treated rats were dead within 45 minutes and all BPI treated rats were dead within 60 minutes.

The results illustrated in Figs. 4a and 4b (where Fig 4a shows the results for both the ischemic and reperfusion phases of the experiment and Fig. 4b shows only the period of reperfusion) show that the administration of $rBPI_{21}\Delta cys$ had the effect of preventing bradycardia resulting from intestinal ischemia/reperfusion.

The results illustrated in Fig. 5 measuring respiratory rate show that the administration of the BPI protein product reduces respiratory depression resulting from the intestinal ischemia/reperfusion injury. The figure only presents data following reperfusion because the respiration rates for vehicle and BPI treated rats were not different prior to opening the occlusion.

The effect of intestinal ischemia and reperfusion on rats treated and untreated with the BPI protein product are set out in Table I below which illustrates the data of Figs. 3a, 3b, 4a, 4b and 5 where t=0 is immediately before reperfusion and t=30 is after 30 minutes of reperfusion.

The results illustrated in Fig. 6 relating to arrythmia duration show that administration of the BPI protein product reduces the duration of heart rate irregularities resulting from intestinal reperfusion. For this analysis the period of time during which obvious heart rate oscillations or arrhythmias were observed was determined for each rat and then averaged. The results were statistically significant with $p<0.001$.

The results illustrated in Fig. 7 show that treatment with the BPI protein product increases survival time in rats suffering from intestinal ischemia/reperfusion injury ($p<0.05$). According to this aspect of the experiment, the time from opening the occlusion until death was recorded for each rat. In all cases death was immediately preceded by a rapid decline in respiration rate and reduction in tidal volume.

TABLE I						
	Blood Pressure (mmHg)		Heat Rate (per min.)		Respiratory Rate (per min.)	
	t = 0	t = 30	t = 0	t = 30	t = 0	t = 30
Vehicle	96 ± 5	37 ± 3	288 ± 2	241 ± 16	51 ± 3	29 ± 3
$rBPI_{21}\Delta cys$	96 ± 5	43 ± 5	284 ± 7	325 ± 9**	56 ± 4	40 ± 4*

t = 0 is immediately before reperfusion, t = 30 is 30 minutes of reperfusion.
* $p < 0.05$ vs. Vehicle, ** $p < 0.01$.

EXAMPLE 2

In an additional experiment with the rat surgical model of experiment 1 two groups of five rats each were surgically prepared and administered with either $rBPI_{21}\Delta cys$, or vehicle in the same manner and dosages as in example 1 except that a blood sample was obtained just prior to death. In addition a third group of five rats was subjected to a sham operation wherein all the surgical procedures were reproduced with the exception that the SMA was never occluded. After death, samples of tissue were obtained from the liver, spleen, and mesenteric lymph nodes. The blood was plated on trypticase soy agar and incubated overnight at 37°C. The tissue samples were then weighed and homogenized and were similarly plated and incubated overnight at 37°C. The next day the number of colonies on the plates were counted visually. The number of bacteria per gram of tissue of each organ is shown in Fig. 8a. The number of rats in which bacteria were detected is shown in Fig. 8b. These results including the sham experiment show that intestinal ischemia/reperfusion results in translocation of bacteria, most likely from the gut. Further, the results show that the administration of the BPI protein product reduced the translocation of bacteria resulting from intestinal ischemia/reperfusion. Analysis of the blood samples indicated no presence of bacteremia in any of the subject animals.

Numerous modifications and variations in the practice of the invention are expected to occur to those skilled in the art upon consideration of the foregoing description of the presently preferred embodiments thereof. Consequently, the only limitations which should be placed upon the scope of the present invention are those which appear in the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Ammons, William Steve et al.

(ii) TITLE OF INVENTION: Method of Treating Conditions Associated with Intestinal Ischemia/Reperfusion

(iii) NUMBER OF SEQUENCES: 2

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Marshall, O'Toole, Gerstein, Murray & Borun
(B) STREET: 6300 Sears Tower, 233 South Wacker Drive
(C) CITY: Chicago
(D) STATE: Illinois
(E) COUNTRY: United States of America
(F) ZIP: 60606-6402

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY INFORMATION:
(A) NAME: Sharp, Jeffrey S.
(B) REGISTRATION NUMBER: 31,879
(C) REFERENCE/DOCKET NUMBER: 27129/32043

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 312/474-6300
(B) TELEFAX: 312/474-0448
(C) TELEX: 25-3856

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1813 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 31..1491

(ix) FEATURE:
(A) NAME/KEY: mat_peptide
(B) LOCATION: 124..1491

(ix) FEATURE:
(A) NAME/KEY: misc_feature

(D) OTHER INFORMATION: "rBPI"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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Glu Thr Leu Asp Val Gln Met Lys Gly Glu Phe Tyr Ser Glu Asn His
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        300                 305                 310

ATA CAG ATC CAT GTC TCA GCC TCC ACC CCG CCA CAC CTG TCT GTG CAG     1110
Ile Gln Ile His Val Ser Ala Ser Thr Pro Pro His Leu Ser Val Gln
    315                 320                 325

CCC ACC GGC CTT ACC TTC TAC CCT GCC GTG GAT GTC CAG GCC TTT GCC     1158
Pro Thr Gly Leu Thr Phe Tyr Pro Ala Val Asp Val Gln Ala Phe Ala
330                 335                 340                 345

GTC CTC CCC AAC TCC TCC CTG GCT TCC CTC TTC CTG ATT GGC ATG CAC     1206
Val Leu Pro Asn Ser Ser Leu Ala Ser Leu Phe Leu Ile Gly Met His
                350                 355                 360

ACA ACT GGT TCC ATG GAG GTC AGC GCC GAG TCC AAC AGG CTT GTT GGA     1254
Thr Thr Gly Ser Met Glu Val Ser Ala Glu Ser Asn Arg Leu Val Gly
            365                 370                 375

GAG CTC AAG CTG GAT AGG CTG CTC CTG GAA CTG AAG CAC TCA AAT ATT     1302
Glu Leu Lys Leu Asp Arg Leu Leu Leu Glu Leu Lys His Ser Asn Ile
        380                 385                 390

GGC CCC TTC CCG GTT GAA TTG CTG CAG GAT ATC ATG AAC TAC ATT GTA     1350
Gly Pro Phe Pro Val Glu Leu Leu Gln Asp Ile Met Asn Tyr Ile Val
    395                 400                 405

CCC ATT CTT GTG CTG CCC AGG GTT AAC GAG AAA CTA CAG AAA GGC TTC     1398
Pro Ile Leu Val Leu Pro Arg Val Asn Glu Lys Leu Gln Lys Gly Phe
410                 415                 420                 425

CCT CTC CCG ACG CCG GCC AGA GTC CAG CTC TAC AAC GTA GTG CTT CAG     1446
Pro Leu Pro Thr Pro Ala Arg Val Gln Leu Tyr Asn Val Val Leu Gln
                430                 435                 440

CCT CAC CAG AAC TTC CTG CTG TTC GGT GCA GAC GTT GTC TAT AAA         1491
Pro His Gln Asn Phe Leu Leu Phe Gly Ala Asp Val Val Tyr Lys
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            445                 450                 455

TGAAGGCACC AGGGGTGCCG GGGGCTGTCA GCCGCACCTG TTCCTGATGG GCTGTGGGGC    1551

ACCGGCTGCC TTTCCCCAGG GAATCCTCTC CAGATCTTAA CCAAGAGCCC CTTGCAAACT    1611

TCTTCGACTC AGATTCAGAA ATGATCTAAA CACGAGGAAA CATTATTCAT TGGAAAAGTG    1671

CATGGTGTGT ATTTTAGGGA TTATGAGCTT CTTTCAAGGG CTAAGGCTGC AGAGATATTT    1731

CCTCCAGGAA TCGTGTTTCA ATTGTAACCA AGAAATTTCC ATTTGTGCTT CATGAAAAAA    1791

AACTTCTGGT TTTTTTCATG TG                                              1813
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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 487 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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Met Arg Glu Asn Met Ala Arg Gly Pro Cys Asn Ala Pro Arg Trp Val
-31 -30                 -25                 -20

Ser Leu Met Val Leu Val Ala Ile Gly Thr Ala Val Thr Ala Ala Val
-15                 -10                  -5                   1

Asn Pro Gly Val Val Val Arg Ile Ser Gln Lys Gly Leu Asp Tyr Ala
               5                  10                  15

Ser Gln Gln Gly Thr Ala Ala Leu Gln Lys Glu Leu Lys Arg Ile Lys
          20                  25                  30

Ile Pro Asp Tyr Ser Asp Ser Phe Lys Ile Lys His Leu Gly Lys Gly
      35                  40                  45

His Tyr Ser Phe Tyr Ser Met Asp Ile Arg Glu Phe Gln Leu Pro Ser
 50                  55                  60                  65

Ser Gln Ile Ser Met Val Pro Asn Val Gly Leu Lys Phe Ser Ile Ser
                 70                  75                  80

Asn Ala Asn Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe
              85                  90                  95

Leu Lys Met Ser Gly Asn Phe Asp Leu Ser Ile Glu Gly Met Ser Ile
         100                 105                 110

Ser Ala Asp Leu Lys Leu Gly Ser Asn Pro Thr Ser Gly Lys Pro Thr
     115                 120                 125

Ile Thr Cys Ser Ser Cys Ser Ser His Ile Asn Ser Val His Val His
130                 135                 140                 145

Ile Ser Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
                150                 155                 160

Ile Glu Ser Ala Leu Arg Asn Lys Met Asn Ser Gln Val Cys Glu Lys
            165                 170                 175
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Val Thr Asn Ser Val Ser Ser Lys Leu Gln Pro Tyr Phe Gln Thr Leu
        180                 185                 190

Pro Val Met Thr Lys Ile Asp Ser Val Ala Gly Ile Asn Tyr Gly Leu
    195                 200                 205

Val Ala Pro Pro Ala Thr Thr Ala Glu Thr Leu Asp Val Gln Met Lys
210                 215                 220                 225

Gly Glu Phe Tyr Ser Glu Asn His His Asn Pro Pro Pro Phe Ala Pro
                230                 235                 240

Pro Val Met Glu Phe Pro Ala Ala His Asp Arg Met Val Tyr Leu Gly
            245                 250                 255

Leu Ser Asp Tyr Phe Phe Asn Thr Ala Gly Leu Val Tyr Gln Glu Ala
        260                 265                 270

Gly Val Leu Lys Met Thr Leu Arg Asp Asp Met Ile Pro Lys Glu Ser
    275                 280                 285

Lys Phe Arg Leu Thr Thr Lys Phe Phe Gly Thr Phe Leu Pro Glu Val
290                 295                 300                 305

Ala Lys Lys Phe Pro Asn Met Lys Ile Gln Ile His Val Ser Ala Ser
                310                 315                 320

Thr Pro Pro His Leu Ser Val Gln Pro Thr Gly Leu Thr Phe Tyr Pro
            325                 330                 335

Ala Val Asp Val Gln Ala Phe Ala Val Leu Pro Asn Ser Ser Leu Ala
        340                 345                 350

Ser Leu Phe Leu Ile Gly Met His Thr Thr Gly Ser Met Glu Val Ser
    355                 360                 365

Ala Glu Ser Asn Arg Leu Val Gly Glu Leu Lys Leu Asp Arg Leu Leu
370                 375                 380                 385

Leu Glu Leu Lys His Ser Asn Ile Gly Pro Phe Pro Val Glu Leu Leu
                390                 395                 400

Gln Asp Ile Met Asn Tyr Ile Val Pro Ile Leu Val Leu Pro Arg Val
            405                 410                 415

Asn Glu Lys Leu Gln Lys Gly Phe Pro Leu Pro Thr Pro Ala Arg Val
        420                 425                 430

Gln Leu Tyr Asn Val Val Leu Gln Pro His Gln Asn Phe Leu Leu Phe
    435                 440                 445

Gly Ala Asp Val Val Tyr Lys
450                 455
```

WHAT IS CLAIMED IS:

1. A method of treating adverse physiological effects associated with intestinal ischemia/reperfusion comprising administering to a subject suffering from the effects of intestinal ischemia/reperfusion an effective amount of a BPI protein product.

2. The method of claim 1 wherein said intestinal ischemia/reperfusion is associated with occlusion of an intestinal artery.

3. The method of claim 2 wherein said intestinal ischemia/reperfusion is associated with occlusion of the mesenteric artery.

4. The method of claim 1 wherein said intestinal ischemia/reperfusion is associated with myocardial infarction.

5. The method of claim 1 wherein said intestinal ischemia/reperfusion is associated with intestinal torsion.

6. The method of claim 1 wherein said adverse physiological effects are cardiac effects.

7. The method of claim 1 wherein said adverse physiological effects are hemodynamic effects.

8. The method of claim 1 wherein the BPI protein product is an amino-terminal fragment of BPI.

9. The method of claim 1 wherein the BPI protein product is $rBPI_{21}\Delta cys$.

10. The method of claim 1 wherein the BPI protein product is administered in conjunction with a pharmaceutically-acceptable diluent, adjuvant or carrier.

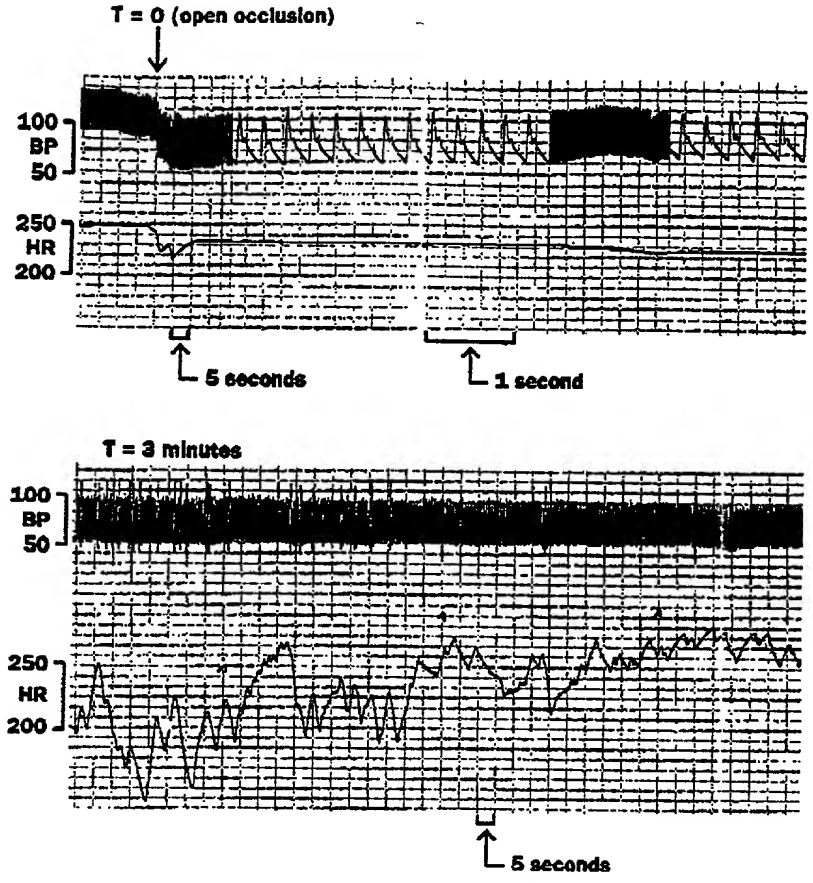
5

METHOD OF TREATING CONDITIONS ASSOCIATED WITH INTESTINAL ISCHEMIA/REPERFUSION

ABSTRACT OF THE DISCLOSURE

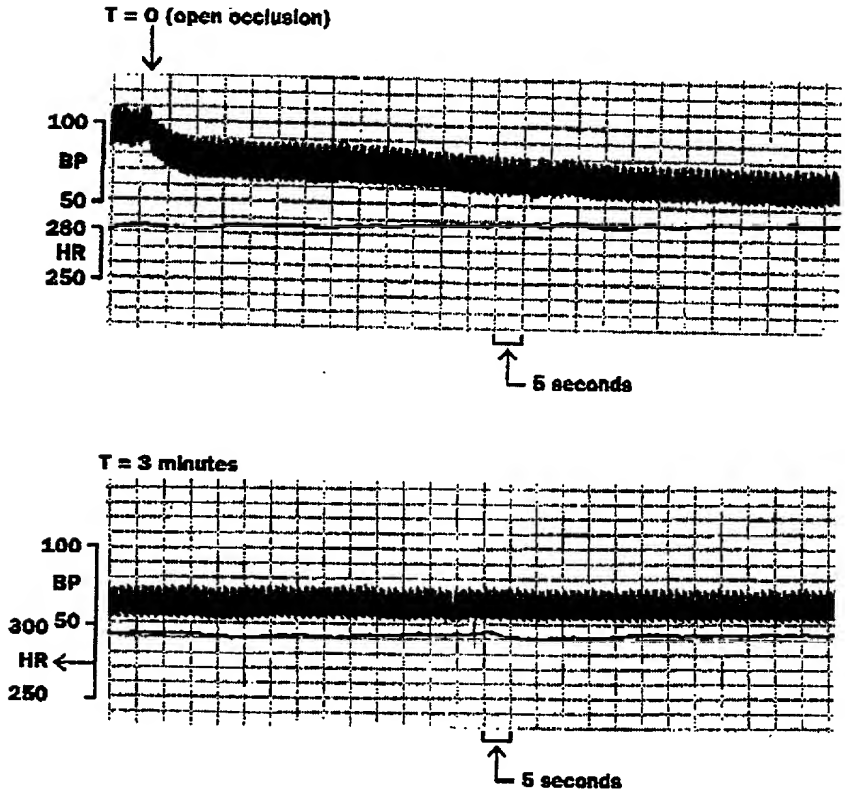
The present invention provides methods of treating adverse physiological effects associated with intestinal ischemia/reperfusion by administering to a subject suffering from the effects of intestinal ischemia/reperfusion an effective amount of a BPI protein product.

FIG. 1



BP = blood pressure, HR = heart rate

FIG. 2



BP = blood pressure, HR = heart rate

FIGURE 3

rBPI$_{21}$ Reduces Hypotension Resulting from Intestinal Ischemia/Reperfusion Injury

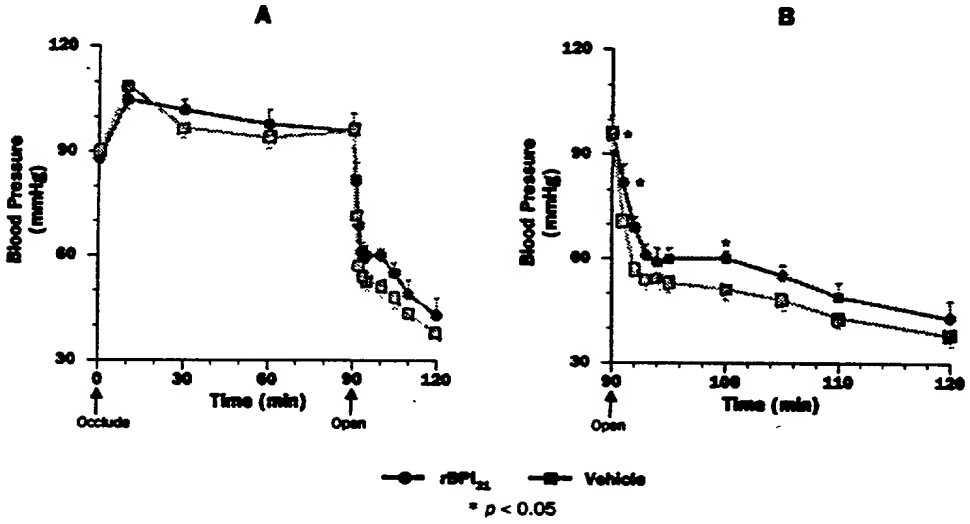


FIG. 3A

FIG. 3B

FIGURE 4

rBPI$_{21}$ Prevents Bradycardia Resulting from Intestinal Ischemia/Reperfusion Injury

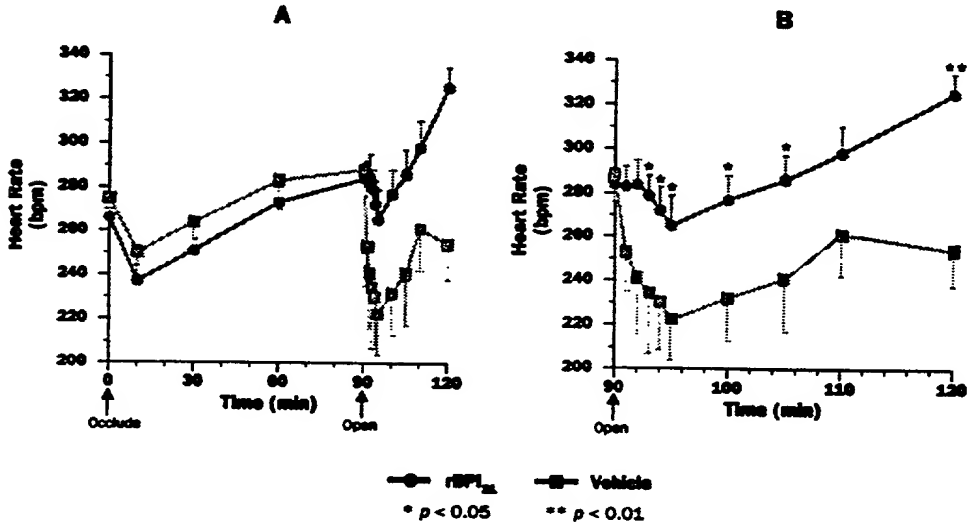


FIG. 4A

FIG. 4B

FIGURE 5
rBPI$_{21}$ Reduces Respiratory Depression Resulting from Intestinal Reperfusion

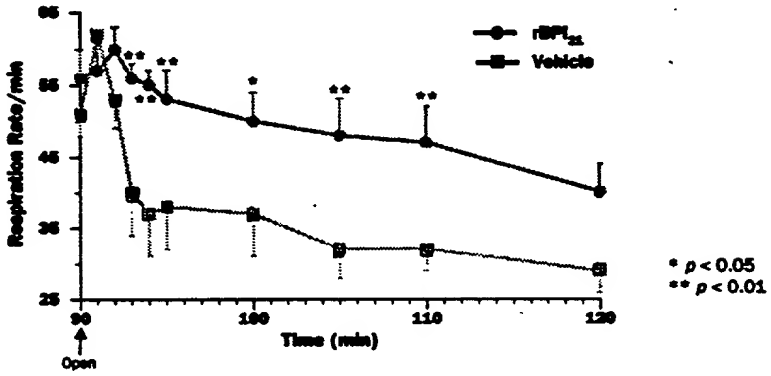


FIG. 5

FIGURE 6
rBPI$_{21}$ Reduces Arrythmias in Intestinal Ischemia/Reperfusion Injury

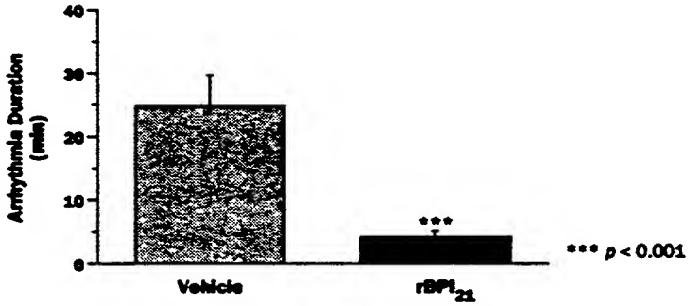


FIG. 6

FIGURE 7
$rBPI_{21}$ Treatment Increases Survival Time

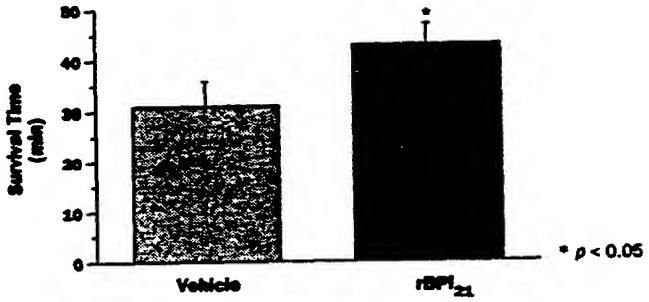


FIG. 7

FIGURE 8
$rBPI_{21}$ Reduces Translocation of Bacteria Resulting from Intestinal Ischemia/Reperfusion

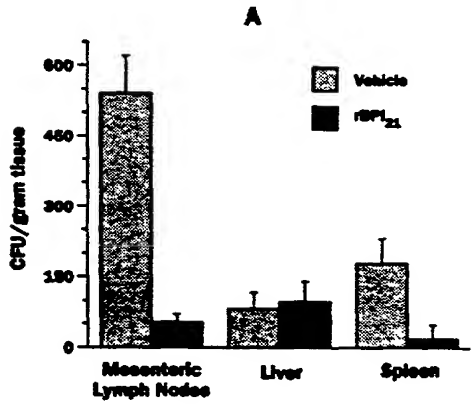


FIG. 8A

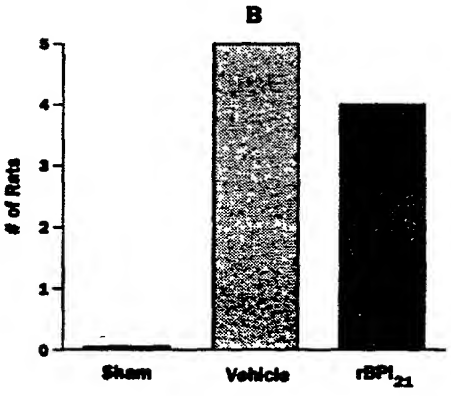


FIG. 8B

Atty. Docket No: 32043

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "**METHOD OF TREATING CONDITIONS ASSOCIATED WITH INTESTINAL ISCHEMIA/REPERFUSION,**" the specification of which (check one): ☐ is attached hereto; ☒ was filed on April 22, 1994 as Application Serial No. _____ _____ and was amended on _____ (if applicable). I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56. I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Claimed
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes ☐ No
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes ☐ No
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status-Patented, Pending or Abandoned)
(Application Serial No.)	(Filing Date)	(Status-Patented, Pending or Abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: I (We) hereby appoint as my (our) attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

Basil P. Mann (18,464)
Alvin D. Shulman (19,412)
Donald J. Brott (19,490)
Owen J. Murray (22,111)
Allen H. Gerstein (22,218)
Nate F. Scarpelli (22,320)
Edward M. O'Toole (22,477)
Michael F. Borun (25,447)
Timothy J. Vezeau (26,348)
Carl E. Moore, Jr. (26,487)
Richard H. Anderson (26,526)
James P. Zeller (28,491)
Lewis S. Gruber (30,060)
William E. McCracken (30,195)
Richard A. Schnurr (30,890)
Anthony Nimmo (30,920)
Christine A. Dudzik (31,245)
Kevin D. Hogg (31,839)
Jeffrey S. Sharp (31,879)
Martin J. Hirsch (32,237)
Richard M. La Barge (32,254)
Jeffry W. Smith (33,455)
Douglass C. Hochstetler (33,710)

Send correspondence to: Jeffrey S. Sharp

FIRM NAME	PHONE NO.	STREET	CITY & STATE	ZIP CODE
Marshall, O'Toole, Gerstein, Murray & Borun	312-474-6300	6300 Sears Tower 233 South Wacker Drive	Chicago, Illinois	60606-6402

Full Name of First or Sole Inventor	Citizenship
William Steve Ammons	U.S.A.
Residence Address - Street	**Post Office Address - Street**
490 Dohrmann Lane	490 Dohrmann Lane
City (Zip)	**City (Zip)**
Pinole (94564)	Pinole (94564)
State or Country	**State or Country**
California	California
Date	**Signature**
☒ 5/24/94	☒ W. Steve Ammons

☒ See second page for additional inventor(s)

See reverse for relevant rules & statutes

Second Joint Inventor, if any	Citizenship
Károly M. Mészáros	Hungary
Residence Address - Street	Post Office Address - Street
2938 Morgan Drive	2938 Morgan Drive
City (Zip)	City (Zip)
San Ramon (94583)	San Ramon (94583)
State or Country	State or Country
California	California
Date ☒ 5/23/94	Signature ☒ Károly Mészáros

Third Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

Fourth Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

Fifth Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

Sixth Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

APPLICABLE RULES AND STATUTES

37 CFR 1.56. DUTY OF DISCLOSURE - INFORMATION MATERIAL TO PATENTABILITY (Applicable Portion)

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and
(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentability defines, to make sure that any material information contained therein is disclosed to the Office.

Information relating to the following factual situations enumerated in 35 USC 102 and 103 may be considered material under 37 CFR 1.56(a).

35 U.S.C. 102. CONDITIONS FOR PATENTABILITY: NOVELTY AND LOSS OF RIGHT TO PATENT

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

(c) he has abandoned the invention, or

(d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than twelve months before the filing of the application in the United States, or

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraph (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or

(f) he did not himself invent the subject matter sought to be patented, or

(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

35 U.S.C. 103. CONDITIONS FOR PATENTABILITY; NON-OBVIOUS SUBJECT MATTER

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negative by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

35 U.S.C. 112. SPECIFICATION (Applicable Portion)

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.